Docket No.: PF-0430-1 DIV

REMARKS

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

Claims 1, 2, 14-19 and 22-25 were originally filed and were subject to a Restriction Requirement. Claims 26-28 were added by a preliminary amendment. Applicants affirm election, with traverse, of original claims 1, 2, and 14, corresponding to the invention of Group I. Applicants reserve the right to prosecute the non-elected claims in subsequent divisional applications.

Justification for the amendments is as follows. The specification has been amended to correct inadvertant typographical and grammatical errors. Claim 1 has been amended to delete "immunogenic" and "biologically-active" fragment language. Step b) of claim 1 has also been amended to recite "a naturally-occurring amino acid sequence having at least 90% amino acid sequence identity to the sequence of SEQ ID NO:1, and which retains glutathione conjugating activity". Justification for the amendment to claim 1 is found throughout the specification, for example, at page 50, Example X, which recites an enzyme assay for measuring glutathione conjugating activity in GSTS. Claim 14 has been amended to delete the term "pharmaceutical" and to correct proper antecedant basis for the term "polypeptide". Claim 25 has been amended to clarify the purpose of the method, to delete fragment language and to correct proper antecedant basis for the term "polypeptide". Claim 23 has also been amended to correct proper antecedant basis for the term "polypeptide" and the phrase "molecule or compound" throughout the claim. No new matter is added by any of these amendments, and entry of the amendments is respectfully requested.

35 USC § 112, First Paragraph, Rejection of Claims 1 and 14

The Examiner has rejected claims 1 and 14 under 35 USC § 112, first paragraph, as containing subject matter which is not described in the specification in such as way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the

claimed invention. The Examiner stated that the claims are drawn to an amino acid sequence having at least 90% identity to the amino acid sequence of SEQ ID NO:1, and that the instant disclosure of a single species of amino acid sequence (SEQ ID NO:1) does not adequately describe the scope of the claimed genus which encompasses a substantital variety of subgenera. The Examiner cited *Reagents of the University of California v. Eli Lilly* with respect to the requirement that a description of a genus of polypeptides may be achieved by means of a recitation of a representative number polypeptides, defined by polypeptide sequence falling within the scope of the genus or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. The Examiner stated that the instant specification fails to provide "definitive structural or functional features of the claimed genus of polypeptides ---- no identifying characteristic or property of the instant amino acids is provided such that one of skill in the art would be able to predictably identify the encompassed molecules as being identical to those instantly claimed". Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus --- the disclosure of specific polypeptide sequences and the ability to screen is insufficient to describe the genus.

Claim 1 has been amended, specifically at step b) to recite "a naturally-occurring amino acid sequence having at least 90% amino acid sequence identity to the sequence of SEQ ID NO:1, and which retains glutathione conjugating activity". Glutathione conjugating activity is described in the specification as the primary enzymatic activity of all GSTs (specification, at p. 1), and a method to measure this activity is described in the specification at page 50, Example X. The structural limitation that all members of the claimed genus must share at least 90% amino acid sequence identity with SEQ ID NO:1 coupled with the functional characteristic that members of the genus must also possess the required enzymatic activity of GST provides sufficient common attributes to the claimed genus that one skilled in the art could readily identify members of the genus. Applicants therefore respectfully request withdrawal of the rejection of claims 1 and 14 under 35 USC § 112, first paragraph.

35 USC § 112, First Paragraph, Rejection of Claim 14

The Examiner has rejected claim 14 under 35 USC § 112, first paragraph, as containing subject matter which is not described in the specification in such a way as to enable one skilled in the

art to which it peratins, or with which it is most nearly connected to make and/or use the invention. In particular, the Examiner stated that the claim is drawn to a pharmaceutical composition comprising the amino acid sequence of SEQ ID NO:1 and that the specification teaches the use of therapeutically effective dose compositions that may consist of GSTS, antibodies, antagonists, etc. --- to treat disorders, including cancer. However, the Examiner stated, one cannot extrapolate the teaching of the specification to the claims because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable. The Examiner then cited various references in support of this position and the fact that many drugs that show promise in the laboratory are ineffective in a clinical setting.

Applicants are fully aware of the general nature of the pitfalls of research in cancer drug therapy. Applicants are not, however, in agreement with the Examiner as to the applicability of these general arguments to the specific case at hand in which GSTs have been implicated in the well known phenomenon of multi-drug resistance (MDR) in cancer and that controlling GST levels during certain drug therapies would be useful in improving the drug treatment regimen (specification, at page 2, lines 7-14). However, in the interest of expiditing the prosecution of the claim, claim 14 has been amended to delete the term "pharmaceutical". Withdrawl of the rejection is therefore respectfully requested.

35 USC § 112, First Paragraph, Rejection of Claims 1 and 14

The Examiner has further rejected claims 1 and 14 under 35 USC § 112, first paragraph, because the specification, while being enabling for SEQ ID NO:1, does not reasonably provide enablement for a sequence at least 90% identical to SEQ ID NO:1. The Examiner stated that these variant sequences are compared using computer programs to determine the degree of identity between a variant sequence and the amino acid aequence of SEQ ID NO:1. The Examiner also noted that sequence identity is defined in the specification as the degree to which the polypeptide sequences are able to maintain biological or immunological activity. However, the Examiner stated, the specification provides neither guidance nor exemplification of how to make a polypeptide which is at least 90% identical to the amino acid sequence of SEQ ID NO:1, a polypeptide that could have at least X number of amino acid alterations, that will function as contemplated. The Examiner then cited Burgess et al and Lazar et al. with respect to the ability of even a single amino acid substitution to alter or eliminate

biological activity in a protein, and Bowie et al. with respect to the teaching that certain amino acid positions within a protein are critical to function and are very intolerant to substitutions.

Applicants first of all point out that the claim recites a "naturally-occurring" amino acid sequence having the described properties and therefore does not encompass any and all polypeptides. The teachings of Burgess et al. and Lazar et al. deal with deliberate, site-directed mutations that were "artificially" created in the laboratory and are not analogous to naturally occurring proteins, such as those claimed, that are profoundly influenced by natural selection. Indeed, Bowie et al., cited by the Examiner, specifically states that proteins are tolerant of numerous amino acid substitutions that maintain protein function, and it is natural selection that permits these substitutions to occur. Conversely, mutations that reduce or abolish protein function are eliminated by natural selection. Bowie states in particular at page 1306, second column, second paragraph, that "proteins are surprisingly tolerant of amino acid substitutions" and at page 1306, second column, third paragraph, that "Residues that are directly involved in protein functions such as binding and catalysis will certainly be among the most conserved" (underline added). The amendment to claim 1, discussed previously, that polypeptides having at least 90% amino acid sequence identity must also possess glutathione conjugating activity, therefore provides ample guidance to one skilled in the art to identify naturally-occurring variants of GSTS having at least 90% amino acid identity to SEQ ID NO:1 and which retain the natural enzyme activity of a GST. Applicants therefore respectfully request withdrawal of the rejection of claims 1 and 14 under 35 USC § 112, first paragraph.

35 USC § 112, Second Paragraph, Rejection of Claims 1 and 14

The Examiner has rejected claims 1 and 14 under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner stated, claim 1 recites an activity without defining what activity is to be measured. It is unclear if a biologically active fragment is a fragment that is antigenically, immunologically, chemotactically, enzymatically, etc., active fragment.

Applicants have amended claim 1 to delete the term "biologically active" and have amended step b) of claim 1 to specifically recite "glutathione conjugating activity". With these amendments,

Applicants believe that claim 1 is now clear and definite and respectfully request withdrawal of the rejection under 35 USC § 112, second paragraph.

35 USC § 102 (b), Rejection of Claims

The Examiner has rejected claims 1 and 14 under 35 USC § 102 (b) as anticipated by Harris et al., Biochem. J. (1991) 278, 137-141. The Examiner stated that Harris et al. disclose an amino acid sequence which has 100% sequence similarity to the portion of the claimed sequence SEQ ID NO:1, amino acids 9-19. The disclosure of Harris et al. is deemed to anticipate the claimed immunogenic and biologically active fragments (of SEQ ID NO:1).

The amendments to claim 1 deleting fragment language have been discussed previously. Harris et al. do not anticipate SEQ ID NO:1. Applicants therefore respectfully request withdrawal of the rejection of claims 1 and 14 as anticipated by Harris et al.

The Examiner has also rejected claim 1 as anticipated by Hillier et al., Genbank Seqeuence Database (Accession AA291397). The Examiner stated that the sequence disclosed by Hillier et al. comprises a sequence which has 100% sequence similarity to the portion of the claimed sequence of SEQ ID NO:1, amino acids 140-207. The disclosure of Hillier et al. is deemed to anticipate the claimed immunogenic and biologically active fragments (of SEQ ID NO:1).

The amendments to claim 1 deleting fragment language have been discussed previously. Hillier et al. do not anticipate SEQ ID NO:1. Applicants therefore respectfully request withdrawal of the rejection of claims 1 and 14 as anticipated by Hillier et al.

Objection to Claim 2

The Examiner has objected to claim 2 as being dependent on a rejected base claim (claim 1), but would be allowable if rewritten in independent form. Applicants believe that with the amendments to claim 1 and arguments presented in rebuttal to the rejections of the claim, all rejections have been overcome, and therefore respectfully request withdrawal of the objection.

Docket No.: PF-0430-1 DIV

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections and rejections. Early notice to that effect is earnestly solicited. Applicants further request that upon allowance of claim 1 that claims 22-28 be rejoined and examined as methods of use of the polypeptides of claim 1 that depend from and are of the same scope as claim 1 in accordance with *Ochiai and Brouwer* (see Commissioner's Notice in the Official Gazette of March 26, 1996).

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Agent of Record.

A fee of $110.00 for a one month extension of time accompanies this response. The Commissioner is hereby authorized to charge Deposit Account No. **09-0108. This form is enclosed in duplicate.**

Respectfully submitted,

INCYTE GENOMICS, INC.

Date: October 18, 2001 David G. Streeter

David G. Streeter, Ph.D.
Reg. No. 43,168
Direct Dial Telephone: (650) 845-5741

3160 Porter Drive
Palo Alto, California 94304
Phone: (650) 855-0555
Fax: (650) 849-8886

Docket No.: PF-0430-1 DIV

Version with markings to show changes made

IN THE SPECIFICATION:

Paragraph beginning at line 3 of page 19 has been amended as follows:

In another embodiment, sequences encoding GSTS may be synthesized, in whole or in part, using chemical methods well known in the art (see Caruthers, M.H. et al. (1980) Nucl. Acids **[Res.]** Symp. Ser. (7)215-223, Horn, T. et al. (1980) Nucl. Acids **[Res.]** Symp. Ser. (7)225-232). Alternatively, the protein itself may be produced using chemical methods to synthesize the amino acid sequence of GSTS, or a fragment thereof. For example, peptide synthesis can be performed using various solid-phase techniques (Roberge, J.Y. et al. (1995) Science 269:202-204) and automated synthesis may be achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin Elmer).

IN THE CLAIMS:

Claims 1, 14, 23, and 25 have been amended as follows:

1. (Thrice Amended) A purified polypeptide comprising an amino acid sequence selected from the group consisting of:

a) an amino acid sequence of SEQ ID NO:1, and

b) a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1, and which retains glutathione conjugating activity

[c) a biologically-active fragment of the amino acid sequence of SEQ ID NO:1, and

d) an immunogenic fragment of the amino acid sequence of SEQ ID NO:1].

14. (Once Amended) A [pharmaceutical] composition comprising the polypeptide [GSTS] of claim 1 in conjunction with a suitable [pharmaceutical] carrier.

23. (Once Amended) A method for using a polypeptide [protein] to screen a plurality [large number] of molecules or compounds to identify a molecule or compound that specifically binds the polypeptide, the method comprising:

(a) combining the polypeptide [protein] of claim 1 with the compound or molecule under conditions to allow complex formation; and

(b) detecting complex formation, wherein the presence of the complex identifies a molecule or compound that specifically binds the polypeptide [protein].

25. (Once Amended) A method of using a polypeptide [protein or a fragment thereof] to purify a molecule or compound which specifically binds the protein from a sample, the method comprising:

a) combining the polypeptide [protein or a fragment thereof] of claim 1 with a sample under conditions to allow specific binding;

b) recovering the bound polypeptide [protein]; and

d) separating the polypeptide [protein] from the molecule or compound, thereby obtaining purified molecule or compound.